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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/204,427	12/03/1998	HEDI HADDADA	8076.102USC1	5504

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/204,427	HADDADA ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,18,23,24 and 26-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *31* is/are allowed.

6)☒ Claim(s) *15,16,18,23,24 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *081303*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed 8-13-03 has been entered. Applicant's arguments filed therein have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-14, 17, 19-22, 25 have been cancelled. Claims 27-32 have been added. Claims 15, 16, 18, 23, 24 and 26-32 are pending and under consideration in the instant invention.

Claim Rejections - 35 USC § 112

1. Claims 15, 16, 18, 23 and 26 remain rejected and claims 27-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

Obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding λ-INF as in claims 15 and 26 is new matter. Obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding IL-2 under the control of an exogenous promoter, early E1A promoter, CMVIE promoter or RSV LTR (claims 16, 18, 23, 27 and 26) is new matter. Applicants point to pg 13, line 4, for support for the claims. However, pg 13, line 4, only describes administering adenovirus encoding IL-2 under the control of an adenoviral late promoter and obtaining regression in 40-50% of patients. The specification as originally filed did not teach or suggest adenovirus encoding λ-INF under the control of the adenoviral late promoter would have the same

effect or cause tumor regression in 40-50% of patients. While the specification contemplated replacing the late promoter, it did not contemplate or suggest the results would also cause 40-50% tumor regression. Therefore, the specification did not contemplate or suggest using an adenoviral vector as broadly claimed to cause tumor regression in 40-50% of patients.

Stimulating the immune system in patients using an adenoviral vector encoding λ-INF as in claim 28 is new matter. Applicants point to pg 13 for support, which only describes administering adenovirus encoding IL-2 to stimulate the immune system. The specification as originally filed did not teach or suggest using adenovirus encoding λ-INF would have the same effect as IL-2 or would stimulate the immune system as claimed. Therefore, the specification did not contemplate or suggest using an adenoviral vector encoding λ-INF as claimed to stimulate an immune response.

Applicants argue the specification suggests other vectors encoding λ-INF or GM-CSF or vectors encoding IL-2 under control of other promoters would have the same result as a vector encoding IL-2 under the control of an adenoviral late promoter. Applicants' argument is not persuasive. No such suggestion can be found. It was well known in the art at the time of filing that vectors encoding different proteins under the control of different promoters had different effects *in vivo* (see Miller, Verma, Deonarain, and Crystal, all of record).

Claims 27 and 29 are new matter because while the specification contemplates replacing the adenovirus late promoter with a ubiquitous, exogenous promoter or an early promoter of the E1A region (pg 14, lines 4 and 22), the specification does not suggest using any promoter exogenous to said adenovirus as claimed or any promoter exogenous to adenoviruses in general as potentially encompassed by the claim (see 112/2nd).

2. Claims 15, 16, 18, 23, 24, 26 remain rejected and claim 27-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

Obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding λ-INF as in claims 15 and 26 lacks written description. Obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding IL-2 under the control of an exogenous promoter, early E1A promoter, CMVIE promoter or RSV LTR (claims 16, 18, 23, 27 and 26) lacks written description.

Viral vectors encoding IL-2 and λ-INF administered intratumorally to inhibit tumor growth were known in the art at the time the invention was made (Nabel, US Patent 6,297,219, Oct. 2, 2001; Barber, US Patent 5,662,896, Sept. 2, 1997). Replication defective adenoviral vectors encoding protein operably linked to the late promoter used to obtain protein expression *in vivo* were known in the art at the time the invention was made (Crystal, US Patent 6,013,638, Jan. 11, 2000; Rosenfeld, 1991, Science, Vol. 252, pages 431-434). The art at the time of filing did not teach administering adenoviral vectors encoding λ-INF or GM-CSF to treat tumors, or using an adenoviral vector encoding the cytokine operably linked to an early or "heterologous" promoter to treat tumors. Thus, procedures for administering adenoviral vectors encoding cytokines capable of causing tumor regression in 40-50% of patients were not well-established. The specification taught obtaining tumor regression in 40-50% of patients using an adenovirus encoding IL-2 under the control of an adenoviral late promoter. The specification did not compare the function of IL-2 with λ-INF or GM-CSF or compare the

function of the late adenoviral promoter with other promoters contemplated in the specification.

An adequate written description of adenoviruses capable of causing tumor regression in 40-50% of patients requires more than a mere reference to potential elements required to obtain such an effect. Instead, a description of the specific combination of promoters and cytokines capable of causing tumor regression in 40-50% of patients is required. It is not sufficient to define an adenoviral vector for gene therapy solely by its principal biological property, i.e. capable of causing tumor regression in 40-50% of patients when injected intratumorally, because disclosure of no more than that is simply a wish to identify the specific combination of cytokines and promoters having that capability. Thus, claiming a method resulting in tumor regression in 40-50% of patients using a replication defective adenoviral vector encoding λINF operably linked to an adenoviral late promoter without suggesting λ-INF would result in tumor regression in 40-50% of patients, without comparing the effect of λ-INF to IL-2 or without comparing the expected results with those obtained using IL-2 is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Similarly, claiming a method resulting in tumor regression in 40-50% of patients using a replication defective adenoviral vector encoding IL-2 operably linked to any other promoter contemplated in the specification without suggesting the other promoters would result in tumor regression in 40-50% of patients, comparing the promoters to the late adenoviral promoter or comparing the expected results with those obtained using the late promoter is not in compliance with the description requirement.

Stimulating the immune system in patients using an adenoviral vector encoding λ-INF as in claim 28 lacks written description for the same reasons. The specification only described stimulating the immune system with adenovirus encoding IL-2 (pg 13, line 1).

Applicants argue the examiner has not established a prima facie case of lack of written description because the examiner has not presented evidence or reasons why a person of skill in the art would not have recognized that the specification described the claimed method. Applicants' argument is not persuasive. The Examiner has established the state of the art, the teachings in the specification and has provided reasons why λ-INF and GM-CSF and promoters other than the adenoviral late promoter do not correlate to IL-2 and the adenoviral late promoter use in the Example on pg 13. Thus, the examiner has established the prima facie case through reasoning based on the lack of teachings in the art taken with the lack of correlation in the specification between the results obtained on pg 13 using adenovirus and IL-2 under control of the adenoviral late promoter with other cytokines or other promoters.

It is unclear why applicants believe the examiners position, that the ability to administer adenoviral vectors encoding cytokines capable of causing tumor regression in 40-50% of patients, was not well-established. In this case, the absence of references relating to the combination of elements in an adenoviral vector capable of causing tumor regression in 40-50% of patients as claimed indicates the claimed invention was not well-established. Applicants have not provided any reasoning why the statement is in error or irrelevant.

3. Claims 15, 16, 18, 23, 24 and 26 remain rejected and claims 27 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being

enabling for administering a replication-defective adenoviral vector intratumorally to a patient such that growth of the tumor is inhibited, wherein said vector encodes IL-2 or λ-INF operably linked to the adenoviral late promoter, does not reasonably provide enablement for obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding λ-INF (claims 15 and 26) or an adenoviral vector encoding IL-2 under the control of an exogenous promoter, early E1A promoter, CMVIE promoter or RSV LTR (claims 16, 18, 23, 27 and 26), treating a tumor using an adenoviral vector encoding GM-CSF (claim 24) or treating a tumor in a patient using an adenovirus encoding IL-2 or λ-INF under control of a promoter other than an adenoviral late promoter (claims 29-31). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claims 15, 16, 18, 23, 24, 26 and 27 are directed toward obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding IL-2 or λ-INF (claims 15 and 26) under the control of an adenoviral late promoter (claim 15) or exogenous promoter (26, 27), specifically the early E1A promoter, CMVIE promoter or RSV LTR (claims 16, 18, 23). Claim 24 is directed toward treating a tumor using an adenoviral vector encoding GM-CSF. Claims 29-31 are directed toward treating a tumor in a patient using an adenovirus encoding IL-2 or λ-INF operably linked to an exogenous promoter.

The combination of promoter, DNA encoding a cytokine and route of administration required to obtain a therapeutic effect against a tumor using adenoviral gene therapy *in vivo* was unpredictable at the time the invention was made. Miller (1995, FASEB J., Vol. 9, pages 190-199) reviewed adenoviral vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the

widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 192, col. 2; page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy continues to be the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviewed adenoviral vectors known in the art for use in gene therapy and discusses problems associated with them (page 241, col. 1). Verma indicated a resolution to vector targeting has not been achieved in the art (see entire article). Crystal (1995, Science, Vol. 270, page 404-410) reviewed adenoviral vectors known in the art and taught, "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (¶ bridging pg 404-405; page 406, col. 2, line 7; page 409).

Viral vectors encoding IL-2 and λ-INF administered intratumorally to inhibit tumor growth were known in the art at the time the invention was made (Nabel, US Patent 6,297,219, Oct. 2, 2001; Barber, US Patent 5,662,896, Sept. 2, 1997). Replication defective adenoviral vectors encoding protein operably linked to the late promoter used to obtain protein expression *in vivo* were known in the art at the time the invention was made (Crystal, US Patent 6,013,638, Jan. 11, 2000; Rosenfeld, 1991, Science, Vol. 252, pages 431-434). The art at the time of filing did not teach administering adenoviral vectors encoding λ-INF or GM-CSF to treat tumors.

The specification taught intratumoral injection of an adenoviral vector encoding IL-2 operably linked to an adenoviral late promoter caused tumor regression in 40-50% of patients and stimulation of the immune system of the patient (¶ bridging pg 12-13).

The specification does not enable obtaining tumor regression in 40-50% of patients using an adenoviral vector encoding λ-INF (15, 26) or an adenoviral vector encoding IL-2 under the control of an exogenous promoter, early E1A promoter, CMVIE promoter or RSV LTR (claims 16, 18, 23, 27 and 26). No examples using an adenovirus encoding λ-INF or GM-CSF were provided. Nor were examples using an adenovirus encoding IL-2 under the control of any other promoter. The specification as originally filed did not teach or suggest adenovirus encoding λ-INF under the control of the adenoviral late promoter would have the same effect as adenovirus encoding IL-2 or cause tumor regression in 40-50% of patients. The specification does not correlate the activity of IL-2 to λ-INF. The specification contemplated replacing the late promoter and lists the RSV LTR, the IE promoter of CMV, and MMTV or metallothionin inducible promoters as possible replacements (pg 14, lines 4-11). However, the specification and the art at the time of filing did not teach the RSV LTR, the IE promoter of CMV, MMTV or metallothionin inducible promoters provided adequate expression of a cytokine to obtain tumor regression. Nor does the specification correlate the late promoter to any other promoter or the amount of expression obtained using the adenoviral late promoter to the amount of expression obtained using the RSV LTR, CMVIE, MMTV or metallothionin inducible promoters such that equivalent levels of expression would be expected. It would have required one of skill undue experimentation to determine how to use an adenovirus encoding λ-INF or adenovirus encoding IL-2 under the control of exogenous promoters to obtain tumor regression in 40-50% of patients as claimed. Therefore, applicants do not overcome the unpredictability in the art by providing

adequate guidance that administering adenovirus encoding λ-INF would cause tumor regression in 40-50% of patients as claimed or that administering adenovirus encoding IL-2 under the control of a promoter other than the late promoter would cause tumor regression in 40-50% of patients.

Treating tumors in patients using an adenoviral vector encoding IL-2 or λ-INF operably linked to an exogenous promoter (29-31) because the specification does not compare the activity of the late promoter with any other promoter.

The specification does not enable using an adenoviral vector encoding GM-CSF to treat tumors (claim 24) because the specification does not teach the level of GM-CSF required to treat a tumor or correlate the level of expression of IL-2 or λ-INF known in the art to inhibit tumor growth with the level of GM-CSF required to obtain an equivalent effect. Without such guidance, it would require one of skill undue experimentation to determine how to use adenovirus encoding GM-CSF to treat tumor cells as claimed.

Applicants argue Miller is irrelevant because it discusses methods not used in the present invention. Applicants argument is not persuasive because Miller discusses the use of adenoviral vectors *in vivo* as being "currently only at experimental levels."

Applicants argue Deonarain is irrelevant because it discusses methods not used in the present invention. Applicants' argument is not persuasive because Deonarain discusses the fact that gene delivery *in vivo* was not predictably used to obtain a therapeutic effect.

Applicants argue Crystal is irrelevant because the present invention overcomes the problem of increasing efficiency cited by Crystal. Applicants' argument is not persuasive because Crystal did not teach how to use an adenoviral vector as broadly claimed to cause tumor regression in 40-50% of patients. Crystal is relevant because

exogenous promoters may not provide the same protein expression efficiency as an adenoviral late promoter.

Applicants' argument regarding two presses releases that state adenoviral vectors encoding IL-2 or γ-INF under the control of CMV promoter in Phase I trials cannot be assessed because the press releases have not been provided. It is noted that applicants' discussion of the press releases does not indicate tumor regression in 40-50% of patients as in claims 15 and 26 (obtaining tumor regression in 50% of cutaneous lymphomas is not equivalent to obtaining tumor regression in 50% of patients having cutaneous lymphomas). Nor does the press relate to administering an adenovirus encoding GM-CSF (claim 24) or an adenovirus encoding IL-2 or γ-INF under the control of the E1A promoter (claims 16, 27, 29). It is unclear whether the adenovirus described in the press releases was described in the specification as originally filed or if modifications were made to the adenovirus to improve expression efficiency.

3. Claims 16, 18, 23 and 26 remain rejected and claims 27, 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 27 is indefinite. An adenovirus having an adenovirus lacking the E1A region and having an adenovirus late promoter (claims 15 and 24) has a mutually exclusive scope as compared to an adenovirus having a promoter exogenous to the adenovirus or an early E1A promoter (claim 27). Thus, claim 27 is not within the scope of claims 15 or 24 and cannot be dependent upon claim 15 or 24 because it does not further limit claim 28. Claims 16, 18 and 23 are indefinite because they depend upon claim 27 and require promoters other than a late adenoviral promoter.

Claim 16 remains indefinite because it does not further limit claims 27, 15 or 24. An adenoviral vector cannot lack the E1A region as in claims 15 and 24 while retaining the early promoter of the E1A region as in claim 16.

Claim 18 is indefinite because if the late promoter operatively linked to the sequence coding for the cytokine as in claims 15 and 24, replacing the late promoter with a promoter exogenous to the adenovirus would also be operatively linked to the sequence coding for the cytokine. Therefore, claim 18 does not further limit claims 27.

Claims 18 and 26 remain indefinite and claims 27, 29 and 30 are indefinite because "exogenous to said adenovirus" is unclear. The term "exogenous" is a relative term and has various meanings depending upon to what it refers. In this case, the specification describes an adenoviral promoter replaced with an exogenous promoter (pg 14). However, it is unclear if the promoter may be exogenous to that particular strain of adenovirus used to make the vector or if all adenoviral promoters are excluded from the claim.

Claim 26 remains indefinite. The claim as amended requires the adenovirus has a deletion in E1A, E1B and E3 and has an adenoviral early promoter or a promoter exogenous to the adenovirus. It is unclear how an adenovirus can lack the E1A, E1B and E3 regions and still have an early promoter because the E1A, E1B and E3 <u>are</u> the early regions. It is unclear whether the "exogenous" adenoviral promoters encompass any adenoviral promoter or is limited to other promoters not present in the strain of adenovirus used to make the vector. If the claim is intended to encompass "exogenous" adenoviral promoters not present in the strain of adenovirus used to make the vector, the claim does not make sense. The "endogenous" promoters could be replaced with "exogenous" adenoviral promoters but then the adenovirus would not lack E1A, E1B

and E3 regions as claimed. Overall, the metes and bounds of the adenovirus are not clear.

Claim 29 is indefinite. An adenovirus having an adenovirus lacking the E1A region and an adenovirus late promoter (parent claim 28) has a mutually exclusive scope as compared to an adenovirus having the late promoter replaced with a promoter exogenous to the adenovirus or an early E1A promoter (claim 29). Thus, claim 29 is not within the scope of claim 28 and cannot be dependent upon claim 28 because it does not further limit claim 28. Claims 30 and 31 are indefinite because they depend upon claim 29 and require promoters other than a late adenoviral promoter.

Conclusion

No claim is allowed.

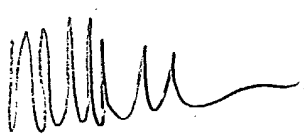
Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER